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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Attn: Docket No. 2004N-0479; Draft Risk Assessment of Streptogramin Resistance in Enterococcus faecium Attributable to the Use of Streptogramins in Animals; Availability—Comments

Dear Sirs,

I have previously prepared estimates of the potential human health impacts of virginiamycin use, and have read with great interest CVM/s draft risk assessment for virginiamycin. I am pleased to submit the attached comments on CVM's Draft Risk Assessment of Streptogramin Resistance in Enterococcus faecium Attributable to the Use of Streptogramins in Animals (Docket No. 2004N-0479).

Overall, CVM's draft risk assessment is a high quality document that provides a great deal of useful information. It documents its data sources, assumptions and calculations, as well as remaining scientific uncertainties, in a way that others can follow and comment on, as a good risk assessment should.

While the attached comments focus on suggestions for improvements, refinements, and extensions, especially in making clearer where the numbers presented refer to actual human health harm vs. a larger set of cases most of which do not involve any actual or potential harm to human health, CVM is to be congratulated on preparing a very useful and well-researched draft.

I would be pleased to further discuss any of these comments and to respond to any questions, and I and look forward to the final version of the risk assessment.

Best Regards,

Louis Anthony Cox, Jr.

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Attachment

2004N-0479

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Comments on FDA-CVM Draft Risk Assessment for Virginiamycin

Louis Anthony Cox, Jr.

INTRODUCTION

FDA's Center for Veterinary Medicine (CVM) has prepared a useful summary and excellent discussion of much current knowledge related to streptogramin-resistant *E. faecium* and has made a useful start toward quantifying potential risks under the assumption that the risks are non-zero. Overall, CVM should be congratulated for preparing a draft risk assessment that provides an explicit account of how numbers useful for risk assessment might be estimated and that acknowledges realistic scientific and modeling uncertainties, including the fact that current microbiological information does not demonstrate that continued use of virginiamycin (VM) necessarily pose any risk to humans. This provides a realistic basis for *contingent* risk assessment, i.e., quantification of hypothesized risks contingent on the assumption that they are non-zero, while recognizing that it is not known whether this assumption is correct.

These comments are intended to suggest refinements in scope, exposition, and details that build on the foundation laid in CVM's draft risk assessment and that may help to further clarify the risks that should be of concern: those that harm humans. We also suggest revisions in exposition and scope that we believe can make the risk assessment more directly useful for informing rational decision-making, e.g., by comparing the human health risks if VM use is continued to human health risks if VM use in not continued. We believe that comparing the probable human health consequences of alternative risk management decisions or policies is an essential component of rational risk-management decision-making, and that the draft risk assessment can be refined and extended to better facilitate such comparisons.

Although the comments that follow emphasize suggestions for improving and clarifying the draft risk assessment, and therefore necessarily contain criticisms and suggested changes in the draft, the overall context for these comments is recognition that CVM has already done a great deal of high-quality work on this risk assessment to date, and is to be congratulated for taking a factual, science-based approach to the challenging problem of VM risk assessment. Thus, we offer the following comments in the spirit of collegial thinking about how best to build on, and in some important places refine (e.g., by focusing specifically on vanA VREF) and extend (e.g., by considering the fraction of cases in which human health harm might actually occur) the good work that has already been done. The basic approach, starting with total numbers of cases and multiplying by a series of fractions estimated from data, is one that we enthusiastically endorse. However, we believe that any sensible approach to risk regulation must consider the potential harm as well as the potential good that regulatory interventions may do to human health, and that the current draft should be extended to consider the potential harm to human health from *not* continuing to use VM, as well as the potential harm from continuing to use it. This will help to more fully inform risk managers about the probable human health consequences of different potential regulatory approaches. It could also provide a basis

for a quantitative Value-of-Information (VoI) analysis of the potential human health benefits from resolving current scientific uncertainties with focused studies (e.g., on the impacts of VM withdrawals on animal health and resulting changes in microbial loads in meats and in human health risks) before implementing risk management actions whose human health consequences might currently be very uncertain in both magnitude and direction.

The following section provides comments on a number of points in the text of the draft risk assessment (section A). Section B discusses the models proposed in the draft.

A. SPECIFIC COMMENTS

HAZARD IDENTIFICATION

p. 10: "Based on microbiological surveys, it is reasonable to assume that a proportion of bowel enterococci at any given time is *E. faecium*, and furthermore, that any member of the human population is potentially at risk of acquiring streptogramin-resistance."

COMMENT: The claim that "any member of the human population is potentially at risk of acquiring streptogramin-resistance" may be needlessly frightening and misleading to members of the public and to decision-makers, due to: (a) ambiguity about what it means for a human (as opposed to a bacterium) to "acquire streptogramin resistance", and (b) use of the word "risk" (which usually suggests potential for harm or loss). While it is indeed reasonable to suppose that some resistant *E.faecium* bacteria (e.g., VREF or SREF) may sometimes pass through people without causing any harm, it is *not* reasonable to assume that most people are put at risk of harm by such transient passage of commensals – or even by longer-lasting inhabitation by commensals, under normal circumstances. Yet, it would be easy for a reader to suppose that "acquiring streptogramin resistance" here means "acquiring a QD-resistant $VREF_A$ infection", as the context of this risk assessment suggests. But then the claim would be both scary and wrong. Most healthy people appear *not* to be at risk of acquiring VREF infections, let alone QD-resistant ones, even if exposed to high doses of *E. faecium* in food. It is usually only seriously debilitated people, typically already hospitalized and affected with multiple other illnesses, who are at risk. This reassuring fact should be emphasized. (It is explained elsewhere in the report, but quotes such as the above suggest that everyone may be at risk, when in fact it is only a very small subpopulation of seriously ill patients who are the focus of potential risk from QD resistance.)

The larger issue here is appropriate and responsible use of language in discussing small hypothetical risks and in communicating model-based speculations about such risks to the public. Studies of risk perception and risk communication show that factors such as dread, unfamiliarity, perceived lack of control, lack of offsetting benefits, and involuntary exposure can greatly inflate a hazard's perceived risk (in some cases making it many times greater than the true or actuarial risk). Antibiotic resistance may be a good candidate for such inflation. Imprecise use of risk language without careful use of

qualifiers such as "hypothetical", "contingent", "harmless", etc. might easily trigger a perception that a small or non-existent risk is a large and serious one. In its present form, the above quote may inappropriately scare people and help to generate a corresponding public demand for action (such as banning or restricting beneficial VM uses) based on a mistaken perception of the risk and of the likely consequences of the action – e.g., even if doing so would actually harm human health. It might be best for CVM to avoid the use of the word "risk" in the above quote (since transient passage *per se* does not entail any loss or harm) and for the passage (and others like it) to be rewritten more neutrally.

CVM's language will be least likely inflate perceived risks if it remains meticulous in stressing the hypothetical nature of the risk, the fact that members of the general public are normally not affected, and the fact that use of VM may have hypothetical human health benefits (risk reductions) much larger than its hypothetical human health costs (risk increases).

To avoid creating misperceptions about the risk to human health from VM and QD use, text such as the one above should be rewritten to emphasize that "acquiring streptogramin resistance" normally entails no harm to humans and is consistent with zero excess risk to human health. Wherever the word "risk" is used to describe events that do not entail any harm to human health (as in the above case of transient passage of a VREF or SREF bacterium through a person with normal immune function), it should be removed and a more explicit description should be substituted (e.g., "any member of the human population might potentially ingest and later excrete streptogramin-resistant bacteria").

p15: "It is well-known that enterococci are commonly found on food commodities. A growing body of literature is increasing our knowledge of the proportion of Enterococcus on food commodities that is *E. faecium*, and the proportion of contaminating *E. faecium* that are also streptogramin resistant."

COMMENT: The hazard identification discussion in the "Identification of Potential Human Health Impact" section starting on page 10 is mainly about *E. faecium* and resistance in general, not about the specific *E. faecium* most relevant for the risk assessment. The specific hazard of concern should not be all *E. faecium*, but rather the comparatively tiny subset with:

1. QD resistance
2. of animal origin
3. and vanA vancomycin resistance
4. in patients who would otherwise be treated successfully with QD.

The report correctly notes that it is the conjunction of vancomycin resistance *and* streptogramin resistance that presents a potential threat. But from this subset of doubly resistant VRE, (a) cases of *E. faecalis* (b) vanB *E. faecium,* (c) vanA *E. faecium* cases

that would not be prescribed Synercid™ in the absence of resistance, and (d) cases for which vancomycin and/or Synercid™ treatment has normal therapeutic effectiveness despite resistance, should all be excluded. Failing to exclude these cases inflates the estimated total number of relevant cases by including those in which QD resistance does not harm human health.

As noted on page 71 of the report, "Unequivocal molecular genetic evidence for animal bacteria origins of streptogramin resistance among human-adapted *E. faecium* has yet to emerge." This statement could be truthfully generalized to "There is no empirical evidence that VM use in animals has any negative impact on human health." It is worth emphasizing that there is no evidence that *vanA VREF bacteria with QD resistance* of animal origin (the relevant hazard) occur *in human patients in ICUs* (the population at risk) at rates that depend on the use of VM in animals. Streptogramin-resistant *E. faecium* per se do not constitute a human health hazard.

Even if VM use did increase the specific exposures of interest, the risk assessment presents no evidence that clinical harm to human health would result. To the contrary, as noted on page 53, "The available data on MIC distribution indicates that most of the resistant isolates in the human surveillance studies have an MIC = 4 µg/mL, a concentration of QD that may still be transiently achievable in serum (Eliopoulis et al., 1998), and the range of MICs generally does not extend beyond 8 µg/mL. It is uncertain whether intermediate resistance (MIC = 4 to 16) should be regarded as acquired resistance (Butaye et al., 2003)." Thus, not only is there is no empirical evidence that VM use has increased human exposures to QD-resistant vanA VREF of animal origin, but there is also no evidence that human health would be compromised even if such exposure did occur.

In summary, an important conclusion from the review of relevant literature and biology is that, despite multiple studies, no data show that VM use in animals has adversely affected human health in any way. It should be stressed in the executive summary and throughout that the legitimate concern that VM use in animals has led to Synercid™ treatment failures lacks empirical support at this time, and that the rest of the risk assessment therefore addresses a purely hypothetical hazard – one that is contingent on the modeling assumption that a risk exists, despite the lack of empirical results showing it. It is responsible and prudent for CVM to consider how large the risk might be if it exists, i.e., a contingent risk assessment is perfectly acceptable and useful, but the public (and decision-makers in the U.S. and abroad who read this document) should be left in no doubt that a careful review of available evidence does not show that any real risk is present and that the entire risk assessment is contingent on a hazard (VM-induced QD resistance in vanA VREF) that may not exist.

EXPOSURE PATHWAYS

p. 16: "The probability of human exposure to streptogramin-resistant *E. faecium* originating from a foodborne pathway can be estimated from the prevalence of resistant *E. faecium* in the community at the time of the intensive care incident."

COMMENTS: It is not clear that this is true. For example, it seems plausible that "The probability of human exposure to streptogramin-resistant *E. faecium* originating from a foodborne pathway" might be zero for ICU patients, independent of "the prevalence of resistant *E. faecium* in the community at the time of the intensive care incident".

The patients in the at-risk population (e.g., AIDS, transplant, chemotherapy, and leukemia patients with multiple serious infectious illnesses) do not necessarily have the same diets and the same cooking and food-handling practices and foodborne exposures as healthy members of the community. Indeed, "at the time of the intensive care incident" will usually mean "during the course of sustained hospitalization and/or closely supervised medical care for other serious conditions" for members of the at-risk population. Assuming that people eating hospital food (or perhaps on IV drips) have the same exposure to bacteria in raw and undercooked meats as members of the community in general seems unwarranted. Thus, it is not clear that this assumption is correct.

Data on esp are relevant here (see e.g., Willems et al., Variant esp gene as a marker of a distinct genetic lineage of vancomycin-resistant Enterococcus faecium spreading in hospitals.Lancet. 2001 Mar 17;357(9259):853-5; and Scott TM, Jenkins TM, Lukasik J, Rose JB., Potential use of a host associated molecular marker in Enterococcus faecium as an index of human fecal pollution. Environ Sci Technol. 2005 Jan 1;39(1):283-7.) These data suggest that VREF causing infections in hospitals generally do *not* reflect VREF rates in the community. For example, Willems et al. (2001) report that "A specific *E. faecium* subpopulation genetically distinct from non-epidemic VREF isolates was found to be the cause of the hospital epidemics in all three continents. This subpopulation contained a variant of the esp gene that was absent in all non-epidemic and animal isolates." It is not clear that QD-resistant VREF cases maong ICU patients should have any particular relation to QD resistant VREF levels in the community. Perhaps a qualifier should be added to the above quote, such as "*if* it is assumed that SREF in the community cause SREF infections in ICU patients *and* that SREF in the community originate in foodborne pathways." But then it should be noted that these qualifying assumptions are not supported – and indeed are undermined – by available data.

RELEASE ASSESSMENT

p. 41: "The question of release in the risk assessment then focuses on the proportions of *Enterococcus* that are the specific strain of interest, *E. faecium*, and the proportion of *E. faecium* that are resistant to virginiamycin or QD."

COMMENT: This definition of release should be further narrowed to address not the proportion of *all E. faecium* that are QD-resistant, but rather the proportion of *vanA VREF* that are (a) QD-resistant; (b) found in human ICU patients; and (c) likely to be of animal origin (e.g., based on marker information such as the esp information considered by Willems et al. and Scott et al.)

EXPOSURE ASSESSMENT

p. 43: "... A clear picture of quantitative human exposures has yet to emerge from the scientific literature or from studies commissioned by CVM. Therefore, the exposure assessment, similar to the release assessment, remains principally qualitative in nature."

COMMENT: The state of exposure assessment information is not so much that a clear picture has yet to emerge, but rather that the picture that has started to emerge so far does not confirm that VM use increases exposure to the *specific* hazard of concern (QD-resistant vanA VREF from animals) in the *specific* population of at-risk patients identified in the report. This is not just a matter of lack of information. Rather, it reflects information that tends to undermine the hypothesis that VM use in animals plays a significant (or detectable) role in human health. As the report notes (p. 53), "Interestingly, the large majority of those studies that report high-level QD resistance in humans (MIC > 16) occur in studies outside of the US. The different MIC distribution between animal and human isolates is *inconsistent with the postulated attribution of human streptogramin resistance to animal sources*" (emphasis added). Similarly, the esp data cited above may tend to weaken the hypothesis that QD-resistant VREF infections in ICU patients originate in VM-exposed animals. In short, the available evidence does not simply leave the exact amounts of exposure unclear, but rather tends to refute they hypothesis that foodborne QD-resistant VREF infections plays a significant role in human health. We believe that it would provide decision makers with useful scientific information if the report more clearly indicated that the exposure assessment does not reveal an absence of relevant information, but rather an absence of support for the hypothesized hazard (i.e., VM-selected QD-resistant vanA VREF) as being an important source of human exposures.

RISK ESTIMATION

p. 75 "The risk estimation integrates the results from the release assessment, exposure assessment, and consequence assessment to produce an overall estimate of the risk. All three elements of the risk assessment process are important contributing factors and should be integrated and considered as a whole when assessing the risk."

COMMENT: The current draft provides an accurate and useful assessment of much available scientific evidence. This evidence is largely negative, in that:

1. The release assessment does not identify any unequivocal (or even strongly suggestive) evidence that there are any releases of VM-related QD-resistant vanA VREF that have been shown to affect the human patients at risk.
2. The exposure assessment does not identify any unequivocal (or strongly suggestive) evidence of non-zero exposures of the relevant human patient populations to VM-selected QD-resistant vanA VREF.
3. The consequence assessment does not show that such exposure, even were it to occur, would cause any adverse human health consequences.

Therefore, an estimate of risk that truly "integrates the results from the release assessment, exposure assessment, and consequence assessment to produce an overall estimate of the risk" should presumably feature *zero risk* as a very plausible value. For example, if we interpret the available evidence as indicating that it is more likely than not (probability of at least 50%) that:

(a) VM-selected QD-resistant vanA VREF are *not* released in sufficient quantities in food products to cause infections in humans (especially after taking into account the food preparation practices and safeguards used for ICU patients and other high-risk patients);
(b) ICU patients with QD-resistant vanA VREF infections do *not* get them via foodborne transmission of VM-selected bacteria (based on esp evidence); and
(c) Even if exposure were to occur at levels sufficient to cause infection, QD resistance would *not* create any incremental adverse health effects (e.g., because of the availability of therapeutic alternatives such as linezolid and because Synercid™ is still effective against the low-MIC resistant types found inhuman patients)

then would be at least an 87.5% probability (= 1 – 0.5*0.5*0.5) that there is zero human health risk posed by VM use in animals. Some such qualifier should be prominently stated in the Risk Estimation section, i.e., policy makers should be aware that zero risk is a very scientifically credible possibility in this case (arguably, the most likely single value), while non-zero risk estimates must rely on unproved conjectures that are not strongly supported by or derived from empirical data showing that a true risk exists.

However, this section of the report reports positive risk estimates despite the lack of any known positive release, exposure, or adverse consequence terms. It does so *not* by integrating the results on these factors, as claimed, but rather by *assuming* that some QD-resistant VREF cases should be blamed on VM use in animals. This assumption appears to have no empirical basis. It is nt supported by or derived from the release, exposure, and consequence sections of the report for the specific bacteria (QD-resistant vanA VREF) and at-risk patients identified as being of concern. In effect, it appears to reflects a decision to blame VM use for some human illnesses despite the lack of empirical support showing that VM use actually causes any adverse health effects in humans.

There is nothing necessarily wrong with such hypothetical calculations (in effect conditioning on a scenario such as "Suppose we blame x% of all cases on VM use, even

though there is no empirical reason to do so"), provided that it is made very clear to readers that this is what is being done. Saying instead that "The risk estimation integrates the results from the release assessment, exposure assessment, and consequence assessment" is potentially misleading in that it suggests that the risk attributed to VM use has some sort of logical and/or empirical basis in the science and data reviewed in these sections, rather than being a "what-if" assumption. To avoid creating a misperception that a real, known risk has been identified and is now being quantified, CVM could add language such as: "Although present data do not indicate a non-zero human health risk from VM use in animals, it is worth considering how large such a risk might be if future evidence were to show that it is not zero."

p. 75: "Probability calculations underlying epidemiological methods are used throughout public health risk assessments in situations where exposures to hazardous agents are recognized and the risks of adverse health effects are statistically associated with "membership" in the exposed group(s)."

COMMENT: It should be made clear in the text that, in this risk assessment, relevant "exposures to hazardous agents" (such as VM-selected QD-resistant VREF in food reaching ICU patients) have *not* been "recognized". To the contrary, available evidence is consistent with absence of such exposures.

Similarly, there is no evidence that any incremental "risks of adverse health effects are statistically associated with 'membership' in the exposed group(s)." Of course, ICU patients with multiple severe infectious diseases, including VREF infections, are a very high-risk group. But within that target population, it has not been shown that those exposed to foodborne VM-selected QD-resistant VREF are likely to be *more* at risk than others. Thus, no excess "risks of adverse health effects" have been "statistically associated with 'membership' in the exposed group(s)." This passage creates an impression that the risk assessment shows that QD resistance causes risks of adverse human health effects, but in fact the data showing this have not been presented. (It is important to avoid confusing the high risks for all members of the target population with the incremental risks potentially created by QD resistance. It is the latter that remains to be demonstrated and quantified.)

Thus, it seems potentially misleading to indicate that probability calculations performed in this section are based on or justified by "calculations underlying epidemiological methods [that] are used throughout public health risk assessments" in similar situations. Rather, the calculations again appear to reflect a decision to blame VM use for some proportion of human health risks (e.g., for purposes of "what-if" analysis) despite the lack of any empirically identified causal relation between them. If this is the situation, the text should make it clear, so as to avoid creating a misperception that a real, empirically demonstrated, risk has been identified and is now being quantified. Adding text to emphasize that this is another "what-if" calculation could help to avoid such potential misunderstandings.

p. 76: "This risk assessment seeks an estimate of the number of cases of streptogramin-resistant *Enterococcus faecium* (SREF) bacteremias where the streptogramin resistance is potentially linked to food animal uses of related streptogramin antimicrobial drugs.

COMMENT: This scope could be improved in the following ways.

1. ***Address only relevant cases.*** The current scope considers *all* SREF bacteremia cases. But for risk assessment purposes, only cases that satisfy these additional conditions should be included:
   a. vancomycin resistant;
   b. vanA;
   c. could be treated with QD (e.g., the patient can tolerate QD);
   d. would otherwise receive QD (rather than linezolid, daptomycin, or other alternatives); and
   e. would otherwise (if not for QD resistance) respond favorably to QD treatment;
   f. does not respond succesfully to QD treatment because of QD resistance.

   By defining its scope as being to develop "an estimate of the [total] number of cases of streptogramin-resistant *Enterococcus faecium* (SREF) bacteremias", the quantitative component of the risk assessment includes many irrelevant cases, meaning cases in which VM use could not cause any human health harm, e.g., because the cases are not candidates to be treated with QD. This is partly recognized later on p. 76, where it is noted that "The human health risk of failing streptogramin treatment, as an adverse health impact from streptogramins used in animal agriculture, includes a 'gate keeping' step of vancomycin resistance because Synercid drug approval is for VREF bloodstream infections". This corresponds to condition (a) in the above list. But the remaining conditions (b)-(f) should also be addressed.

   The scope should either be narrowed to include only cases that might actually result in harm to human health, i.e., cases satisfying the above conditions, or else the text should be revised to make it very clear to all readers that the "risk" being quantified consists largely of cases with no possibility of adverse human health effect – not the usual definition of risk. Otherwise, a reader might naturally suppose that the estimated cases being reported have something to do with harm to human health, and on this basis be inclined to support "risk management decisions" (such as bans or restrictions on VM use) that would not be supported if it were made clear that most of the estimated cases being reported do not involve any harm to human health.

2. ***Address potential for human health harm.*** The current scope does not correctly include occurrence of human health harm – an essential component of human health risk. For example, suppose, for purposes of clear discussion only, that QD resistance has *no effect* on human health, i.e., that streptogramin-resistant vanA VREF cases have exactly the same effects on human health as streptogramin-susceptible vanA VREF (e.g., because the resistant cases are still treated effectively by therapeutic doses of Synercid™). In this case, the health risk attributed to QD resistance

logically should be *zero* (since, by assumption, there is no incremental health harm.) Yet, the "number of cases of streptogramin-resistant *Enterococcus faecium* (SREF) bacteremias" would *not* necessarily be zero. Thus, this is not the right quantity to estimate to represent risk of human health harm caused by QD resistance. Even without making the extreme simplifying assumption of no harm from resistance, it is clear that the potential for harm to occur (which is presumably much less than 100% even if it is greater than 0%) should be addressed in quantifying "risk" of harm.

3. ***Consider changes, not absolute levels.*** The risk assessment should be based on the *change* in human health harm caused by QD-resistant vanA VREF bacteria from VM use. The number of cases in which there is a change in human health harm may be much smaller than the total number of SREF cases.
4. ***Cleary identify "what-if" analyses and distinguish them from empirically-based risk estimates.*** The number of cases that are "potentially linked to food animal uses of related streptogramin antimicrobial drugs" may be much larger than the number of cases *caused* by use of VM. While the meaning of "potentially linked to" is not stated here, it appears later that it means "arbitrarily attributed to". That is, the actual calculations decide to blame 10% or 100% of cases on VM use in food animals for purposes of what-if analysis, although there is no empirical support for either fraction. But what-if analyses with hypothetical attribution fractions should not be conflated with being "potentially linked to food animal uses" in the real world.
5. ***Address risk from alternative decision options.*** The current draft does not compare the human health risks caused by alternative risk management interventions (e.g., continuing *vs.* discontinuing VM use.) Thus, the results do not provide decision-makers with information needed to compare and choose among competing options based on their probable human health consequences. In particular, estimating hypothetical risks from the *status quo* (continued use of VM) does not tell readers whether changing the *status quo* would increase or decrease risks. It would be very useful to extend the analysis to *consider how changing VM use would change human health risks*, taking into account the causal impacts of VM use on multiple pathways (such as necrotic-enteritis-positive flocks) affected by the changes. For example, is it true that reducing VM use would increase the loads of VM-susceptible bacteria in animals and meat products, and if so, how would this affect human health? A scope that only looks at some effects (e.g., impacts on resistant bacteria) and not other, potentially larger, ones (such as impacts on susceptible bacteria) provides an incomplete, potentially misleading, basis for informing decisions.

p. 77: "There are several ways that publicly available data sources can be used to estimate the number of VREF cases in the US during a given year."

COMMENT: Number of VREF cases is a superset of the relevant quantity: vanA VREF cases that experience treatment failure (or compromised treatment) because of VM-related QD resistance. Using this superset of the relevant cases inflates the resulting risk estimate by including cases in which there is no human health harm from QD use.

p. 83: "Low et al. (2001) reported that about 82% of the vancomycin-resistant *Enterococcus* isolates were also susceptible to quinupristin-dalfopristin (QD)

streptogramins. A crude estimate of the percent of the VRE that have some level of QD resistance (or "SRE") is 100-82 = 18%."

COMMENT: This QD resistance fraction is for *all* VRE, not for vanA VREF, which are the specific bacteria of interest.

p. 83: "The second assumption made for this study is that *all* streptogramin resistance in the non-hospitalized community is due to food animal uses of virginiamycin."

COMMENT: No justification is given for this assumption, nor does it seem plausible. For example, classification error, companion animals, sewage, and other pathways presumably account for some of the reported resistance level. (The Scott et al., 2005 paper states: "The human fecal pollution marker designed in this study targets a putative virulence factor, the enterococcal surface protein (esp), in Enterococcus faecium. This gene was detected in 97% of sewage and septic samples but was not detected in any livestock waste lagoons or in bird or animal fecal samples. Epidemiological studies in recreational and groundwaters have shown enterococci to be useful indicators of public health risk for gastroenteritis". Thus, it appears that *E. faecium* in humans may not necessarily be of animal origin. For QD-resistant *E. faecium* specifically, it has been reported that "There was no correlation between receipt of virginiamycin or weight gain and presence of quinupristin/dalfopristin-resistant strains" (Donabedian S, Thal LA, Bozigar P, Zervos T, Hershberger E, Zervos M., Antimicrobial resistance in swine and chickens fed virginiamycin for growth promotion. J Microbiol Methods. 2003 Dec; 55(3):739-43.) Thus, it seems inappropriate to simply assume that "*all* streptogramin resistance in the non-hospitalized community is due to food animal uses of virginiamycin", even though it seems plausible that some fraction might be due to this source. It would be desirable to estimate this fraction, if community QD resistance levels continue to be used in the risk assessment. Alternatively, if QD resistance levels in vanA VREF cases in hospitalized patients are used, then the esp data of Willems et al. should be considered. In either case, the fraction of QD resistance in human patients that comes from VM use in animals could well be zero, and this should be acknowledged.

p. 84: "For the purposes of informing risk management decisions, a central estimate of 10% is used for the probability of origination in food pathways. ... The parameter distributions are for illustration purposes only, and other estimates can be proposed and analyzed to provide alternative risk scenarios."

COMMENTS:

1. Although described here as being "for illustration purposes only", these parameter distributions directly drive the reported conclusions of the risk assessment. Similarly, the phrase "for the purposes of informing risk management decisions" is misleading when it is applied to the 10% central estimate, as that number is actually entirely hypothetical and part of a distribution "for illustration purposes only". The only information that it provides "for the purposes of informing risk management

decisions" is not valid empirical information (about the real world), but hypothetical "what-if" information. Again, there is nothing wrong with this, except that it should be made absolutely clear wherever the results are presented that they are only hypothetical what-if calculations, not realistic risk estimates dictated by real-world facts and data.

2. The risk assessment in its current form, while containing much useful scientific and risk-related information, is not really suitable as a decision support document and should not be offered as appropriate "for the purposes of informing risk management decisions". To adequately inform rational risk management decisions, the risk analysis would have to be extended do the following: (a) Identify multiple alternative decision options to be compared; (b) Assess the probable human health consequences of each alternative (considering both risk increases and risk reductions, transmitted via susceptible bacteria as well as resistant bacteria, and considering the impacts of changes in VM use on necrotic enteritis and other animal illnesses that may affect the microbial loads of bacteria such as Campylobacter and Salmonella reaching consumers in food, as well as patients affected by SREF). (c) Identify the decision option(s) giving the most desirable probability distribution of human health consequences that can be achieved. The current risk assessment does not carry out these steps, and hence does not provide some essential information for risk management decision-making.

p. 84: "Finally, Willems et al. (2000), studies on VREF isolates in Europe estimated that the upper bound on transfer from food animals to hospitalized groups is 11.5%. For the purposes of informing risk management decisions, a central estimate of 10% is used for the probability of origination in food pathways"

COMMENTS:

1. The Willems et al. upper bound of 11.5% suggests that 10% is *not* a "central estimate", but is close to being an *upper-bound* estimate.
2. The subsequent decision to run the range up to 20% does not seem to be justified by any empirical data.
3. The most likely single value should be 0%, not 10% (since there is a finite probability that the true risk is zero). No justification is given for assigning 10% a greater probability density than 0%.
4. Since the selected probability distribution is said to be offered "For the purposes of informing risk management decisions", it should acknowledge that 0% is a plausible (indeed, the most likely) value.

p. 85: "Risk assessments, by necessity, often rely on the application of data and results of studies for purposes other than the original purpose of the study. For example, some of the health statistics databases were assembled to survey health trends and utilization, not to estimate rates, odds ratios or other 'risk' indices. As it is often practiced in regulatory and industry settings, risk assessment is a meta-analytic science..."

COMMENT: The report should not lose sight of the fact, or let readers form an impression, that the quantitative part of this risk assessment is based on anything other than a what-if analysis (e.g., assuming 10% or 100% for origin in the food pathway) for which there is no empirical support for the specific bacteria (QD-resistant vanA VREF) and at-risk population identified in the report. The data do not show any human health harm or exposure via the postulated route. To select 10% (or 100%) as an attribution fraction is purely a what-if analysis, based on a postulated scenarion, not on an application of "a meta-analytic science", or any other kind of science. It does not "rely on the application of data and results of studies for purposes other than the original purpose of the study", or on any other data. Rather, it simply replaces the empirical evidence of no detectable effect with an assumption of an effect. As previously stated, there is nothing wrong with doing what-if and contingent analyses – indeed, they can be very valuable in bounding potential risks – but it is essential to be straightforward in explaining and emphasizing that this is what has been done, and to avoid language that might convey the impression that the scenarios considered are driven by data if they are not.

p. 88: "Data provided to the FDA indicate that 356,800 counting units of Synercid (*USyn*) were sold in 2001."

COMMENT: These data are obsolete. Since 2001, Synercid has been increasingly displaced by linezolid. Using old data to predict future risks inflates the predicted risk estimates.

TYPO NOTE: In equation 10,p. 88, the "×" sign should be a division sign.

p. 89: "The final step in this chain is to calculate the proportion of these cases that might be Synercid resistant stemming from community as opposed to ICU sources of resistance."

COMMENT: The proportion should not be calculated for *all* of these cases, but for the subset (VM-selected QD-resistant vanA VREF of animal origin) that are relevant for this risk assessment.

p. 94: "Using this assumption, the results show that the mean number of attributable SREF cases might range from 2 to 39 in one year (Table 6-5)."

COMMENT: *Zero should be included in the range of plausible values.* (The subjectively estimated triangular uncertainty distribution incorrectly assigns a probability density of zero to zero cases for the food pathway, rather than a discrete finite probability mass.) The modeling assumption that the mean number is positive should not be treated as certain, as it is here. Reporting only a positive range is highly misleading to potential decision-makers. Stating the results in such a way that zero risk is excluded, rather than

emphasizing that it is consistent with all available data, tends to undermine the credibility of this generally high-quality document by making it appear that the conclusions do not fully reflect the data.

p. 100: "... The average risk to a random *hospitalized* member of the US population, the most relevant 'at-risk' population, of having SREF attributable to animal uses of virginiamycin and that may result in impaired Synercid therapy, ranges from 6 chances in 100 million to 1.2 chances in 1 million in one year; however, if the food pathway attribution is assumed to be 100%, then the estimated mean number of cases of SREF in humans per year attributable to animal uses of virginiamycin would increase 10-fold."

COMMENTS:

1. Again, it is essential for credibility that *zero risk should be included in this range.* There is no good scientific reason to exclude zero risk of SREF attributable to animal uses of virginiamycin and that may result in impaired Synercid therapy. Arguably, it is the most likely single value.
2. This range is for the estimated risk *of a resistant case*, not the estimated *excess* risk caused by VM use. It is incorrect to call it the risk "of having SREF attributable to animal uses of virginiamycin".
3. It is misleading to refer to the risk presented here as risk of a SREF case "that may result in impaired Synercid therapy", as it includes *all* cases, not just those that would be prescribed Synercid and that would subsequently suffer impaired effectiveness of Synercid therapy.
4. It should be noted that if the food pathway is assumed to be 0%, or very small (as esp evidence suggests may be realistic), then the risk will be zero or small.

In short, the estimated numbers presented here do *not* correspond to the written description, but to a larger set of cases that includes irrelevant cases (e.g., not just vanA cases, not just cases that would be treated with QD, not just cases that result in compromised treatment, etc.) Therefore, this summary does not present an accurate characterization of the *specific* risk (of VM-related QD-resistant vanA VREF cases in which QD resistance causes clinical harm) that the report earlier identifies as being the risk of interest. This should be clarified in the text, or the smaller numbers corresponding to the specific risk of interest should be presented.

B. GENERAL COMMENTS AND DISCUSSION OF MODELING APPROACH

Definition of Risk

The FDA-CVM study defines risk as the annual number of animal-attributable cases of SREF among cases of VREF. This is the maximum possible number of annual cases that might be considered as potentially treatable with Synercid, not the number that

actually is treated with Synercid. This definition has limited utility for the following reasons:

The study assumes that the resulting quantity is caused by use of VM in food animals, and that, accordingly, the quantity reflects the annual human health benefit that would occur if VM were not used. But this ignores the fact that:

- *Synercid is not always effective,* even when QD resistance is not an issue.
- *Synercid is not always prescribed.* It is not the only treatment available. Its prescription rate is declining while the prescription rate of alternatives is increasing. (Linezolid is an attractive alternative that is gaining rapidly in popularity; see http://www.aafp.org/afp/20020215/663.html.)
- *Synercid resistance in vanA VREF does not always cause clinical harm.* "Resistant" does not mean "impervious". Therapeutic levels of Synercid may kill QD-resistant vanA VREF. A weakness of the definition is that no true human health consequence, such as excess illnesses, mortalities, or QALY's is provided.
- *VM resistance declines very gradually* (over several years) after withdrawal from food animals.
- *Illnesses that are "attributable to" VM use in animals may not be caused by VM use in animals.* For example, the infecting bacteria may be *E. faecalis* misclassified as *E. faecium*; QD-resistant strains may have originated in hospital sewage rather than in animals, etc.

Risk Assessment Models

The FDA-CVM analysis provides three models for determining the risk as they define it. Each model is of the form:

$R = c_{VREF} \times P_{SR,VREF} \times p_{trans}$

$P_{SR,VREF}$ = the probability of streptogramin resistance, given that the E. faecium infection is vancomycin resistant (mean = .022)

p_{trans} = food attributable fraction (mean = 0.10)

Let us define the generic variable, c_{VREF}, to denote the estimated mean annual number of cases of VREF potentially treatable by Synercid. The three FDA-CVM models present different ways of computing c_{VREF}. Below, each method is illustrated, along with the mean values of the components; in addition, these models are compared to an alternative model developed by Cox and Popken (2004)..

Model 1 (ICU Bloodstream infections):

$c_{VREF} = n_{inf} \times P(VREF|ICU) = 104{,}372.5 \times .012413 =$ **1,296.58**

n_{inf} = estimated number of ICU infections/year
P(VREF|ICU) = the probability of an ICU infection being VREF

Model 2 (Synercid prescriptions):

$c_{VREF} = U_{Syn} / \lambda_{Rx} / t_{Rx} = 356{,}800 / 3 / 7.6 =$ **15,649**
U_{Syn} = counting units of Synercid sold in 2001
λ_{Rx} = treatment rate in counting units/day
t_{Rx} = treatment duration in days

Model 3 (Septicemia Cases)

c_{VREF} = Sep x P(VREF|ICU) = 315,000 x .012413 = **3,909.94**
Sep = # septicemia cases/year
P(VREF|ICU) = the probability of an ICU infection being VREF

Cox and Popken

$c_{VREF} = n_{VRE}$ x P(VanA VREF|VRE) = 37,482.6 x .61 = **22,864.39**
n_{VRE} = estimated annual number of VRE cases
P(VanA VREF|VRE) = Probability that a VRE infection is vanA type E faecium.

The following table compares the different models.

	Model 1	Model 2	Model 3	Cox and Popken
c_{VREF}	**1,296.58**	**15,649**	**3,909.94**	**22,864.39**
$P_{SR,VREF}$	.022	.022	.022	0.009
p_{trans}	.10	.10	.10	.12 (chicken only)
Exogenous case proportion	NA	NA	NA	0.17
QD effectiveness	NA	NA	NA	0.72
Prescription[1] rate	NA	NA	NA	0.922^{t+6}
VM resistance [2]after withdrawal	NA	NA	NA	$e^{-.057t}$

Table 1. Comparison of Component Mean Values by Method

[1] The index, t, represents quarters, where t = 0 is Q1 2002
[2] The index, t, indicates the number of quarters after withdrawal

Notes:

The declining prescription rates and resistance rates used by Cox and Popken incorporate time varying dynamics. .

CVM's Models 1 and 3 ignore the fact that *only vanA VREF is treated with Synercid.*(approximately 73% to 83% of VREF in the US is vanA)

CVM's Model 2 assumes 2001 sales values for Synercid. But Synercid use is likely declining sharply. It also assumes that *all* Synercid is used for treating VREF and that all units of Synercid sold in 2001 were used in 2001. These and other assumptions are not wel supported; indeed, as CVM states,"The results of Model 2 are the expressed opinion of the FDA."

As shown in Table 1, the Cox and Popken model is the most conservative in its estimate of the total number of cases (c_{VREF}). But because it carries out calculations for *relevant* cases, meaning cases in which human health harm occurs (e.g., mortalities that might be prevented by removing VM). By contrast, CVM's models address a larger set of cases that includes many irrelevant ones (e.g., vanB cases, cases not prescribed QD, cases with no adverse effects on treatment, etc.). Therefore, the Cox-Popken analysis eventually produces smaller numbers than CVM's. These smaller numbers are not directly comparable to CVM's, as they refer to cases of actual human health harm, which CVM did not estimate. But they suggest that considering cases of actual human health harm would yield smaller numbers than CVM's. Readers of the CVM risk assessment should be made aware that the numbers reported do *not* necessarily represent human health harm or potential harm, and thus they provide a (perhaps extreme) upper bound on the range of possible risks. The true risks might be much smaller and could very possibly be zero. For example, as indicated earlier, if there is at least a 50% probability that each of three multiplicative factors (for release, exposure, and consequence) independently equals zero, then there is at least an 87.5% probability that human health risk is zero.